

**U.S.S.N. 09/942,959**

**Osbakken *et al.***

**AMENDMENT**

**REMARKS**

Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 50-1213.

Claims 67-69, 73-85, and 87-113 are pending in the instant application. Claim 75 is amended to provide proper antecedent basis. Claim 86 is cancelled without prejudice or disclaimer to delete an inadvertent duplication of claim 80. No amendments have been made to obviate prior art and no new matter has been introduced.

A Supplemental Information Disclosure Statement is also filed on the same day herewith under separate cover. The Examiner's attention is directed to U.S. Patent No. 6,576,224, U.S. Application Nos. 10/193,081, and 10/231,804, and published PCT Application WO 01/002024.

**OBJECTIONS TO THE SPECIFICATION**

The Office Action objects to the embedded hyperlink and browser-executable code within the specification. Amendments to the Specification at pages 2-3 and pages 11-12 delete any and all hyperlink and browser-executable code to comply with MPEP § 608.01.

**OBJECTIONS TO THE CLAIMS**

The Office Action objects to 86 as a duplication of claim 80. Claim 86 has been canceled herein, thus the objection is rendered moot.

**REJECTION OF CLAIMS 67-69 and 73-113 UNDER 35 U.S.C. §103(a)**

Claims 67-69 and 73-113 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rubin *et al.* (U.S. Patent No. 5,925,334) in view of Schmitt *et al.* (U.S. Patent No. 4,950,477) and Saunders Manual of Medical Practice (referred to hereinafter as Saunders Manual). The Office Action alleges that Rubin *et al.* teaches a surfactant mixed with an aerosolizing agent to promote mucus clearance and further, that the use of surfactants lowers surface tension to enhance

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distribution and spreading of other medications to the lower respiratory tract, such as a surfactant and an antibiotic and a surfactant and an inhaled anti-inflammatory agent for conditions such as sinusitis. The Office Action alleges that Schmitt *et al.* teaches administration of non-antimicrobial antibiotic such as amphotericin B by aerosol spray to prevent pulmonary infection. It is also alleged that Schmitt *et al.* teaches particle size of polyene between 0.5  $\mu\text{m}$  and 8.0 $\mu\text{m}$  are important for the polyene to reach and be retained in the lungs. The Office Action alleges that the Saunders Manual teaches the state of the art regarding treatment of sinusitis including antibiotics, decongestants, mucolytics, other ciliator activators, nasal corticosteroids, antihistamines and saline.

The Office Action then alleges that it would have been obvious to a person of ordinary skill in the art to combine the surfactants/antibiotics/anti-inflammatory agents of Rubin *et al.* with the non-antibiotic antimicrobial agent and particle size of Schmitt *et al.* and the other agents disclosed in the Saunders Manual such as antibiotics, decongestants, mucolytics, nasal corticosteroids, and antihistamines to treat sinusitis with reasonable expectation of preparing formulations with multiple active agents which make the treatment more effective and potent. Further, the Office Action alleges that one of ordinary skill in the art would be motivated to optimize the osmotic pressure, pH and NaCl equivalency of the composition by routine experimentation to include a wider range of different drugs.

This rejection is respectfully traversed.

#### **Relevant Law**

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious.

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Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

## **THE CLAIMS**

The claims of the instant application are directed to methods of treating sinusitis. Independent claim 67 is directed to a method comprising the step of nasally administering a pharmaceutical composition of betamethasone and a surfactant to a mammal diagnosed or suspected of having sinusitis, where the composition is formulated for nasal administration and has a surface tension effective for deposition, penetration or retention in the nasal sinuses.

Claims 68, 69 and 73-113 are dependent on claim 67 and thus encompass the required elements of claim 67. The dependent claims further specify species of surfactants, the hydrophile-lipophile (HLB) balance of surfactants and characteristics of the composition including surface tension, osmolality, pH, NaCl equivalency, and particle size, and administration of the composition with a nebulizer. Dependent claims also specify the addition of a second agent such as an anti-histamine, a mast cell stabilizer, a non-antibiotic anti-microbial agent, an anti-leukotriene, an anti-viral, an antiseptic, a non-steroidal anti-inflammatory, a

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combination of at least two antibiotics, an agent for treating nasal polyps, an anticholinergic agent and combinations thereof and particular species thereof.

**Differences Between the Claims and the Teachings of the Cited References**

**Rubin et al. (US 5,925,334)**

Rubin *et al.* is directed to methods to promote airway clearance for applications including mucus clearance, meconium aspiration syndrome and sleep apnea. Rubin *et al.* teaches the use of surfactants as lubricating agents to reduce airway obstruction (column 10, lines 5-9). Additionally, Rubin *et al.* teaches the use of surfactants for airway clearance in the lower respiratory tract (*e.g.* lungs; column 10, lines 10-34).

Rubin *et al.* does not teach or suggest methods of treating sinusitis with compositions of betamethasone and a surfactant where the composition is formulated with a surface tension effective for deposition, penetration or retention in the nasal sinuses. On the contrary, the methods of Rubin *et al.* are directed to the distribution and spreading of medications to the lower respiratory tract (column 10, lines 14-19). Rubin *et al.* offers no teaching or suggestion of medications and/or surfactants delivered to the sinuses. Further, Rubin *et al.* does not teach or suggest methods of treating sinusitis. Although Rubin *et al.* discusses the use of surfactants with anti-inflammatory agents in patients with conditions of upper respiratory obstruction, the use of the surfactant is "to enhance the distribution of inhaled anti-inflammatory agents...to the lower respiratory tract" (column 10, lines 26-34). The treatment of Rubin *et al.* is not for the treatment of the patients' sinusitis but rather to clear the airway obstruction and treat the lower respiratory tract such as the lungs. Further, Rubin *et al.* does not teach or suggest particle size, osmolality, pH, NaCl equivalency, hydrophile-lipophile balance or surface tension characteristics in methods for treating sinusitis or in any other condition or treatment. *Alt F10 S*

**Schmitt et al. (U.S. Patent No. 4,950,477)**

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Schmitt *et al.* is directed to the use of polyene for prevention of a pulmonary fungal infection. Schmitt *et al.* teaches the administration of an aerosol spray of polyene or a pharmaceutically acceptable derivative such as amphotericin B (column 1, lines 60-66; column 4, lines 55-58). Schmitt *et al.* teaches the administration of particles of polyene such that the particles reach and are retained in the lungs (column 2, lines 50-63).

Schmitt *et al.* does not teach or suggest methods of treating sinusitis with compositions of betamethasone and a surfactant where the composition is formulated with a surface tension effective for deposition, penetration or retention in the nasal sinuses. In contrast, the methods taught by Schmitt *et al.* are directed to delivering medications to the lungs. For example, the particle sizes taught by Schmitt *et al.* are for delivery of polyenes to the lungs (column 2, lines 50-63). Schmitt *et al.* also does not teach or suggest methods for treatment other than pulmonary infection, nor medications other than polyene. Moreover, this reference does not teach or suggest the use of particle size for medications other than polyene nor any other condition. Schmitt *et al.* also does not teach or suggest osmolality, pH, NaCl equivalency, hydrophile-lipophile balance or surface tension characteristics in methods for treating sinusitis or in any other condition or treatment.

#### **Saunders Manual**

Saunders Manual teaches general practices for diagnosing and treating sinusitis. It does not teach or suggest the use of surfactants, nor the use of compositions with effective surface tension for deposition, penetration or retention of compounds in the nasal sinuses. Further, Saunders Manual does not teach or suggest particle size, osmolality, pH, NaCl equivalency or hydrophile-lipophile balance in methods for treating sinusitis.

#### **ANALYSIS**

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

**The combination of teachings of Rubin et al. with the teachings of Schmitt et al. and the Saunders Manual does not result in the instantly claimed methods.**

Combining the teachings of Rubin *et al.* with the teachings of Schmitt *et al.* and the Saunders Manual does not result in the instantly claimed methods of treating sinusitis with compositions of betamethasone and a surfactant formulated with a surface tension effective for deposition, penetration or retention in the nasal sinuses. Rubin *et al.* does not teach or suggest methods of treating sinusitis nor does Rubin *et al.* teach methods with compositions of betamethasone and a surfactant formulated with a surface tension effective for deposition, penetration or retention in the nasal sinuses.

Schmitt *et al.* does not cure this defect. Schmitt *et al.* does not teach or suggest methods using betamethasone with a surfactant nor any other treatments for sinusitis. As discussed above, Schmitt *et al.* only teaches the treatment of pulmonary infections with a polyene. Further, Schmitt *et al.* does not teach methods using compositions with effective surface tension for deposition, penetration or retention in the nasal sinuses. Schmitt *et al.*, like Rubin *et al.*, teaches only delivery of a medication to the lungs. Thus, neither Rubin *et al.*, nor Schmitt *et al.*, single or in combination, teaches or suggests methods using a composition with a surface tension effective for deposition, penetration or retention in the nasal sinuses.

Saunders Manual also does not cure this defect. The manual provides no teaching or suggests alone or which can be used in combination with Rubin *et al.* and Schmitt *et al.* to arrive at the instantly claimed methods. Saunders Manual does not teach or suggest compositions using surfactants, nor methods of delivering medications to the nasal sinuses. Although Saunders Manual lists medications such as anti-inflammatories, as well as decongestants, antihistamines, antibiotics and mucolytics for treating sinusitis, there is no teaching or suggestion of compositions of such medications in compositions with a surfactant nor with effective surface tension for deposition, penetration or retention in the nasal

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sinuses. Further, there is no motivation to combine the teachings of surfactants of Rubin *et al.* with Saunders Manual to arrive at the instantly claimed methods since Rubin *et al.* teaches surfactants only for clearance of airway obstruction to allow delivery of medications to the lungs. As discussed above, none of the references cure this defect since there is no teaching or suggestion in Rubin *et al.*, Schmitt *et al.*, nor Saunders Manual of using compositions with an effective surface tension to deliver medications to the sinuses. Since this is a required element of claim 67 and claims 68, 69 and 73-113 dependent thereon, the combination of Rubin *et al.*, Schmitt *et al.* and Saunders Manual does not result in the instantly claimed subject matter.

**Rebuttal to specific arguments set forth in the Office Action**

Based on the arguments above, and in light of the fact that each encompasses the required elements of claim 1, the dependent claims are deemed to be free of this rejection. Applicant wishes to rebut arguments made in the Office Action with regard to specific dependent claim elements allegedly found in the art.

**1. The combination of Rubin *et al.* with Schmitt *et al.* and Saunders Manual does not teach or suggest particle size for use in the instantly claimed methods**

The Office Action alleges that Schmitt *et al.* teaches particle size and that one of ordinary skill in the art would have been motivated to combine the surfactants/antibiotics/anti-inflammatories of Rubin *et al.*, with the particle size of Schmitt *et al.*, and the other medications of Saunders Manual to arrive at the claimed methods to treat sinusitis. As discussed above, Rubin *et al.* teaches surfactants for airway clearance to allow the delivery of medications such as anti-inflammatories to the lungs. Rubin *et al.* does not teach or suggest particle size nor methods of using compositions with surfactants and medications for with a surface tension effective for deposition, penetration or retention in the nasal sinuses. Schmitt *et al.* does not cure this defect because Schmitt *et al.* only teaches particle size of polyenes for treating fungal infection and only teaches

particle size for retention in the lungs. Schmitt *et al.* teaches that particle size is important because particles smaller than 0.5  $\mu\text{m}$  are exhaled and not retained in the lungs whereas particles greater than 8.0  $\mu\text{m}$  do not reach the periphery of the lungs and therefore are not effective in treating or preventing the infection (column 2, lines 50-63). Saunders Manual does not teach or suggest particle size nor methods to deliver medication to the sinuses. Thus, there is no teaching or suggestion in Schmitt *et al.*, alone or in combination with the other cited references, that would result in the instantly claimed methods using compositions with particle sizes for deposition, penetration or retention in the nasal sinuses.

**2. Reliance on common knowledge**

The Office Action alleges that one of skill in the art would be motivated to optimize the osmotic pressure, pH and NaCl equivalency of the composition by routine experimentation to include a wider range for different drugs. Applicant respectfully submits that there is no basis for such an assertion and that the Examiner has provided no evidence to support this claim. The Examiner is reminded that MPEP 2144.03 states:

Official notice unsupported by documentary evidence should only be taken by the examiner where the facts are asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known. *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970).

There must be some basis to show that facts allegedly known in the art are common knowledge and/or a rationale must be presented to demonstrate the scientific reasoning supporting such an assertion. MPEP 2144.03 also sets forth:

Ordinarily, there must be some form of evidence in the record to support an assertion of common knowledge. See *Lee*, 277 F.3d at 1344-45, 61 USPQ2d at 1434-35 (Fed. Cir. 2002); *Zurko*, 258 F.3d at 1386, 59 USPQ2d at 1697.

The examiner must provide specific factual findings predicated on sound technical and scientific reasoning to support his or her conclusion of common knowledge. See *Soli*, 317 F.2d at 946, 37 USPQ at 801; *Chevenard*, 139 F.2d at 713, 60 USPQ at 241.

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Although the characteristics of osmotic pressure, pH and NaCl equivalency, with regards to other compositions may be known in the art, there is no teaching or suggestion in the art to indicate that these are characteristics of choice to be manipulated in methods for treating sinusitis. Further, there is no teaching or suggestion in the art of how to alter such characteristics which result in methods effective for treating sinusitis. The instantly claimed methods specify ranges of osmotic pressure, NaCl equivalency, and pH for use in the claimed methods of treating sinusitis. The Examiner has presented no evidence which suggests the specified ranges were common knowledge in the art for use in treating sinusitis.

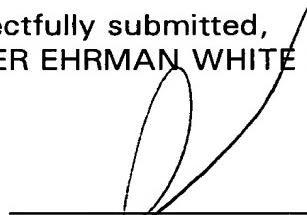
The Examiner has failed to set forth a *prima facie* case of obviousness. Applicant respectfully requests that the rejection be reconsidered and withdrawn

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In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,  
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